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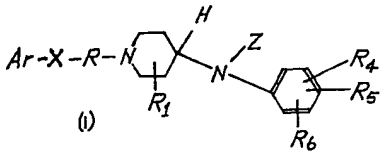
(54 ACYLAMINOPIPERIDINES, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(71) We, SCIENCE UNION ET Cie, SOCIÉTÉ FRANCAISE DE RECHERCHE MEDICALE, a French Societe en nom collectif, of 14, rue du Val d'Or, 92150 Suresnes, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:–

This invention relates to 4-acylamino piperidines, to processes for their preparation and to pharmaceutical compositions containing them.

The present invention provides compounds of the general formula



(I)

in which

R_1 is a hydrogen atom or a lower alkyl group;

R is an alkylene chain having from 2 to 4 carbon atoms which may be substituted with one or more lower alkyl groups;

X is a sulphur atom or a group $-N(R_2)-$

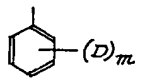
in which R_2 is a hydrogen atom, a lower alkyl carbonyl group, a lower alkenyl group or a lower alkyl group;

Z is the acyl group of an alkane carboxylic acid having up to 10 carbon atoms;

each of R_4, R_5 and R_6, which are the same or different, is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group or a lower alkylene dioxy group; and

Ar is

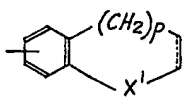
(a) a phenyl group of the general formula



in which each D is a halogen atom or a lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, lower alkylthio, carboxy, lower alkoxy carbonyl, nitro, amino, lower alkylamino, di(lower alkyl) amino, lower acylamino, sulphonamido, lower alkylamino sulphonyl, di(lower alkyl) amino sulphonyl, lower alkyl sulphonyl, amino carbonyl, cyano, trifluoro methyl or lower alkylene dioxy group, and

m is 0 or an integer from 1 to 5;

(b) a bicyclic group of the general formula

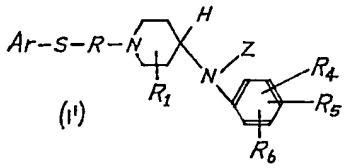


in which X' is an imino group NH and p is 0, 1 or 2, or

X' is a sulphur atom and p is an integer from 1 to 3, and the broken line indicates an optional double bond; or

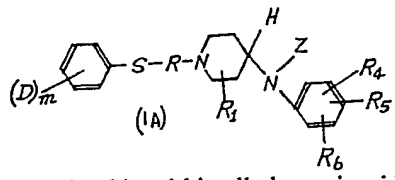
(c) a thienyl group which may be substituted with a lower alkyl group.

Preferred compounds of the general formula I are those of the general formula



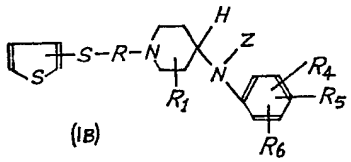
(I')

in which Z, R, Ar, R_1, R_4, R_5 and R_6 have the meanings given above, especially the phenylthio alkylene piperidines of the general formula



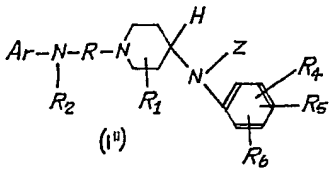
(IA)

and the thienylthio alkylene piperidines of the general formula



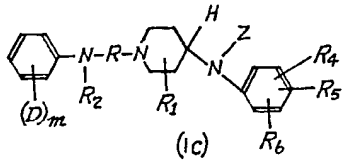
(IB)

and those of the general formula



(I'')

in which R, R_1, R_2, R_4, R_5, R_6 and Z have the meanings given above, especially the compounds of the general formula



(Ic)

in which D, R, R_1, R_4, R_5, R_6, Z and m have the meanings given above and R_2 is a hydrogen atom or a methyl, ethyl, allyl or acetyl group.

The compounds of general formula I are basic and may be converted into salts by adding mineral or organic acids, preferably physiologically tolerable acid.

When R_1 is a lower alkyl group or when R is a lower alkylene group substituted by an alkyl group, the compounds include at least one asymmetric carbon atom and may therefore exist in the form of resolved optically-active isomers or geometric diastereoisomers. Resolution may be carried out by example, by salification with an optically-active organic acid such as a carboxylic acid, a sulphonic acid or a phosphoric acid.

In the context of the present specification, the term "lower alkyl" is used to designate an alkyl group having from 1 to 6 carbon atoms in a straight or branched chain which may be substituted by a hydroxy, lower acyloxy, lower alkoxy, or di(lower alkyl) amino group.

Examples of such lower alkyl group are the methyl, ethyl, isopropyl, sec. butyl, neo-pentyl, tert. butyl, n-hexyl, β-hydroxy ethyl, and diethyl amino-ethyl groups.

The term "halogen" is used to designate a fluorine, chlorine, bromine or iodine atom. Fluorine and chlorine atoms are preferred.

The term "lower alkenyl" designates an unsaturated hydrocarbon group having a carbon-carbon double bond and from 2 to 10 carbon atoms in a straight or branched chain, for example an allyl, methallyl, isopentenyl, dimethylallyl, butenyl, triallylmethyl or pentadienyl group.

The term "lower alkynyl" designates a hydrocarbon radical having a carbon-carbon triple bond and from 2 to 6 carbon atoms, for example an ethynyl, prop-2-ynyl, prop-1-ynyl, or 1-methylbut- 2-ynyl group.

The acyl group is preferably derived from a lower alkyl carboxylic acid, the alkyl chain of which may be substituted. Examples of preferred acyl groups are those derived from acetic, propionic, butyric, di-n-propyl acetic, isovaleric, caproic, diethyl aminoacetic, pimelic, succinic, and β-ethoxy- β-ethoxy acetic acids.

When Ar is a bicyclic group, it may be an indolinyl, dihydro indolinyl, tetrahydro indolinyl, benzo thienyl, dihydro benzothienyl, benzothio pyranyl or thiachromenyl group.

When Ar is a substituted thienyl group it may be a 3-methyl thienyl-2-, 4-methyl thienyl-2-, 5-ethyl thienyl or 2-isopropyl thienyl group.

As mentioned above, the compounds of the general formula I which include at least one asymmetric carbon may be resolved into their optical isomers by salification with an organic optically-active acid. Examples of suitable optically-active acids are d-tartaric acid, 1-cetogulonic acid, ascorbic acid, 1-methoxy acetic acid, abietic acid, N,N-dimethyl tartramic acid, d-campho sulphonic acid, d-glucose- 1-phosphoric acid

and d-glucose- 1,6-phosphoric acid.

The compounds of the general formula I may also be salified by adding a mineral or organic acid, preferably a physiologically tolerable acid. However, acids which are not physiologically tolerable form salts which may be useful for isolating, purifying or characterizing the compounds.

Examples of useful acids are hydrochloric, hydrobromic, hydroiodic, sulphuric, nitric, phosphoric and sulphurous acids; formic, acetic, valeric, lauric, benzoic, naphthoic, and pamoic acids; *p*-bromo benzene sulphonic, ehtane sulphonic, isethionic and methane sulphonic acids; nicotinic, 5-methyl thiazol carboxylic, thienyl carboxylic and indolyl acetic acids; and ethanol phosphoric acid.

The compounds of the general formula I and the physiologically tolerable acid addition salts thereof are endowed with interesting pharmacological properties, especially anti-hypertensive properties. In contrast to the strong neuroleptic and analgesic properties exhibited by the known 4-amino piperidines previously described in French Medical Patents Nos. 2429, 2430 and 2431, they do not exert any analgesic effect and may be wholly differentiated therefrom. They find therapeutic use in human and veterinary medicine as drugs for treating hypertension without the risk of noxious side effects on the central nervous system.

Due to their powerful pharmacological properties the following compounds are especially preferred:

1-[2- (thienyl- 2-thio)- ethyl]- 4-(N-phenyl-N-propionylamino)-piperidine;

1-[2-(2,6-dimethylphenylthio)-ethyl]-4-(N-phenyl-N-propionylamino)-piperidine;

1-[2-(phenyl amino)- ethyl]- 4-(N-phenyl-N-propionyl amino)- piperidine;

1-[2-(N-phenyl- N-methyl amino)- ethyl]-4-(N-phenyl-N-propionylamino)-piperidine;

1-[2-(2,6-dichloro phenyvl amino)- ethvll-4-(N-phenyl-N-propionylamino)-piperidine;

1-[2-(N-phenyl N-acetylamino)-ethyl]-4-(N-phenyl-N-propionylamino)-piperidine;

1-[2-2,6-dimethylphenylamino)-ethyl]- 4-(N-phenyl-N-propionylamino)-piperidine;

1-[2-(N-phenyl-N-allylamino)-ethyl]-4-(N-phenyl-N-propionylamino)-piperidine;

and the acid addition salts thereof.

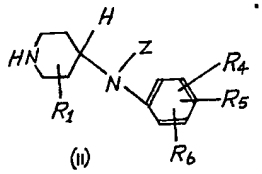
In view of the pharmacological properties of the compounds of the general formula I, the present invention also provides pharmaceutical compositions which comprise as the active ingredient a compound of the general formula I or a physiologically tolerable acid addition salt thereof in admixture or conjunction with a pharmaceutically suitable carrier.

Such pharmaceutical compositions may be in a form suitable for oral, parenteral, sublingual, or rectal administration, for example in the form of ampoules, phials, multidose flasks, tablets, coated tablets, dragees, soft gelatine capsules, granulates, drops, syrups, sublingual tablets, or suppositories.

The pharmaceutical compositions according to the present invention may be prepared by conventional processes. The inert carrier is preferably water or a saline solution, previously sterilized for injectible solutions or suspensions; talc, calcium carbonate, magnesium phosphate, magnesium stearate, formolated casein, or gelatine for tablets or capsules; cocoa butter of polyethylene glycol stearates for suppositories; sugar, syrup of arabic gum, glycerol or water for liquid preparations.

The useful posology may vary broadly depending on the age and the weight of the patient and the severity of the disease to be treated. In general, it ranges from 1 to 250 mg of compound of the general formula I or a salt thereof per unit dosage and from 2 to 1000 mg per day in man.

The present invention also provides a process for preparing compounds of the general formula I which comprises reacting a 4-amino piperidine of the formula



(II)

in which R_1, R_4, R_5, R_6 and Z have the meanings given above, with a compound of the formula

Ar – X – R – Y (III)

in which Ar, X and R have the meanings given above and

Y is a halogen atom or the acyl group of a lower alkylmr an aryl-sulphonic acid.

The resulting compound of the general formula I may, if desired, be salified by adding a mineral or organic acid, or resolved into its optically-active isomers or diastereo isomers by chemical or physical methods, or acylated by means of a carboxylic acid having from 1 to 10 carbon toms or a functional derivative thereof when X is an imino group –NH–.

The process is preferably carried out in an inert solvent in the presence or in the absence of a base.

The inert solvent is preferably an aprotic polar solvent, for example dimethyl for-

mamide, dimethyl acetamide, dimethyl sulfoxide, hexamethyl phosphoramide or acetonitrile, or a halogenated solvent, for example methylene chloride or dichlor ethane, an aromatic hydrocarbon, for example benzene, toluene or xylene or a cycloalkane, for example cyclopentane or cyclohexane.

The compounds of the formula II are preferably derived from an acyl group which may be easily split off, for example methane sulphonic acid, ethanesulphonic acid, benzene sulphonic acid, *p*.toluene sulphonic acid and bromobenzenesulphonic acid. There may also be used halogen derivatives, for example a chloride or a bromide. When a bromide is used, it is especially advantageous to carry out the condensation in the presence of an alkali metal iodide and in a dialkyl ketone as solvent, for example acetone, methylisobutyl ketone, or methylethyl ketone.

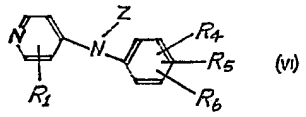
As the base which may be present, there may be used a lower trialkylamine, for example triethylamine, a di(lower alkyl) arylamine, for example dimethylaniline or a pyridine base, for example pyridine, collidine, lutidine or 4-dimethylamino-pyridine. pyridine.

The base may also be an excess of the amino piperidine of the formula II or the inert solvent itself when it is basic, for example dimethyl formamide or hexamethylphosphoramide.

The present invention also provides a process for preparing compounds of the general formula I which comprises condensing an arylalkyl ester of the formula

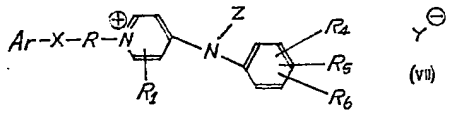
Ar – X – R – Y (III)

in which Ar, X, R and Y have the meanings given above with a 4-amino pyridine of the formula



(VI)

in which R_1, Z, R_4, R_5 and R_6 have the meanings given above, to produce a pyridinium salt of the formula



(VII)

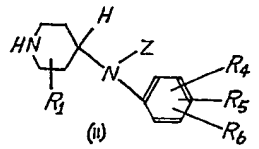
and reducing the latter by catalytic hydrogenation or with an alkali metal complex hydride to obtain a compound of the general formula I.

According to this process the reduction step is preferably carried out either by hydrogenation in the presence of palladium or platinum, or with potassium or sodium borohydride or lithium aluminium hydride.

The compounds of the general formula I may also be prepared by a process which comprises condensing an aryl lower alkanol of the formula

Ar – X – R – OH (VIII)

in which Ar, X and R have the meanings given above with a 4-amino piperidine of the formula

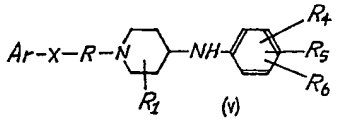


(II)

wherein R_1, R_4, R_5, R_6 and Z have the meanings given above in the presence of a hydrogenation catalyst to produce a compound of the general formula I.

The hydrogenation catalyst is preferably Raney nickel and more preferably Raney nickel WR.

The compounds of the general formula I may also be prepared by a process which comprises submitting an aryl lower alkyl piperidine of the formula



(V)

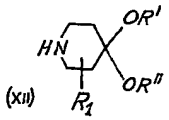
in which Ar, X, R, R_1, R_4, R_5 and R_6 have the meanings given above, to the action of an acylating agent derived from an alkyl carboxylic acid having from 1 to 10 carbon atoms.

The acylating agent is preferably a halide of an alkyl carboxylic acid, for example the acid chloride, or the alkyl carboxylic acid itself in the presence of a dehydrating agent, for example a dilower alkyl- or a dicycloalkyl- carbodiimide.

The compounds of the formula V may conveniently be produced by condensing a compound of the formula

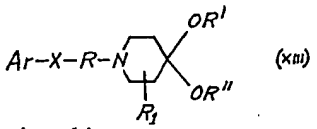
Ar – X – R – Y (III)

in which Ar, X, R and Y have the meanings given above, with a blocked piperidone of the formula



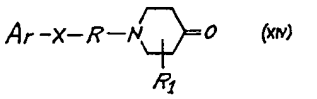
(XII)

in which R_1 has the meaning given above and each of R′ and R″, which may be the same or different, is a lower alkyl group or R′ and R″ together form a lower alkylene chain having 2 or 3 carbon atoms, to produce an aryl-lower alkyl piperidine of the formula



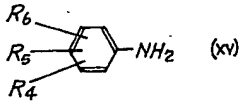
(xiii)

hydrolysing this compound in acid medium or submitted to the action of a carbonyl compound to produce the corresponding piperidone of the formula



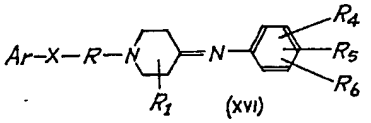
(xiv)

condensing the latter with an arylamine of the formula



(xv)

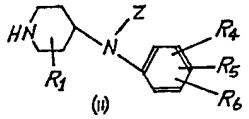
in which R_4, R_5 and R_6 have the meanings given above, to produce an imine of the formula



(xvi)

and treating this compound with a reducing agent, for example an alkali metal complex hydride, to obtain the compound of the formula V.

The present invention provides another process for preparing compounds of the general formula I which comprises reacting a 4-amino piperidine of the formula

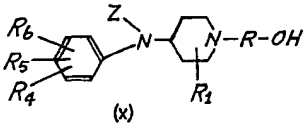


(ii)

in which R_1, Z, R_4, R_5 and R_6 have the meanings given above, with a compound of the formula

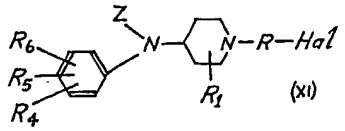
Y – R – OH (IX)

in which Y and R have the meanings given above, to produce a 4-amino piperidine-alkanol of the formula



(x)

submitting the latter ot the action of a halogenating agent to produce the corresponding halide of the formula



(xi)

in which Hal is a halogen atom and reacting the latter with an aryl derivative of the formula

Ar – X – H (IV)

in which Ar and X have the meanings given above, to obtain the compound of the general formula I.

The halogenating agent is preferably a halogenated derivative of an oxyacid, for example phosphorus tribromide, phosphorus oxychloride, sulfuryl chloride or thionyl chloride; or an arylsulphonyl halide, for example p. toluene sulphonylchloride or a metallic halide, for example vanadium chloride.

Condensation of the halide of the formula XI with the aryl derivative of the formula IV is preferably carried out in a basic medium, for example in the presenceof an alkaline reagent such as sodium hydroxide or potassium hydroxide.

The starting compounds of the general formula III may be produced by reacting a thiophenol of the formula Ar – SH or from an arylamine of the formula Ar – NHR' with an epoxy lower alkane to produce an aryl-lower alkanol of the general formula

Ar – X – R – OH (VIII)

which is then reacted with a halogenating agent, for example phosphorus tribromide, hydroiodic acid or *p*.toluene sulphonyl chloride.

The 4-amino piperidines of the general formulae II and V may be obtained according to processes described in the literature, for example the process described in the German Patent No. 1,470,357.

The following Examples illustrate the invention.

EXAMPLE I

1-[2-(thienyl- 2-thio)- ethyl]- 4-(N-phenyl-N-propionyl amino)- piperidine

Step A 2-thienylthiol

100 ml tetra hydrofuran and 10.6 ml thiophene are placed in a three-neck flask. The mixture is cooled to −40°C and 59 ml of a 2.35M solution of butyl lithium in n-hexane are then added over about 5 minutes. After one hour of reaction while keeping the temperature at about −30°C, the mixture is cooled to −70°C and 4.1 g sulphur are added. The mixture is allowed to stand for one and a half hours. The reaction mixture becomes brownish. It is poured into a stirred mixture of water and ice and the resulting aqueous phase is decanted off. The organic phase is extracted with few ml water. The aqueous solutions are united, cooled to about 0° and rendered acidic by

adding a 4N solution of sulphuric acid. The aqueous solution is extracted three times with ether, the ether phases are separated, washed with water, dried over sodium sulphate, filtered and evaporated to dryness. The dry residue is purified by fractionated distillation under reduced pressure – 3.6 g 2-thienylthiol are recovered. The pure compound boils at 60–65°C under 15 mm Hg.

2-Thienylthiol is used as such for the next step of the synthesis.

Step B

1-[2-(thienyl- 2-thio)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine

In a flask fitted with a mechanical stirrer there are successively placed 3.6 g 2-thienyl thiol, 3.6 g sodium hydroxide and 15 ml water. To the resulting suspension, 6 g 1-(β-chloro- ethyl)- 4-(N-phenyl- N-propionyl amino)- piperidine hydrochloride dissolved in 25 ml water, are added. The whole mixture is heated to reflux for 3 hours. An oily precipitate appears which is extracted three times with ether at ambient temperature. The ether phases are united, washed with aqueous sodium carbonate then twice with water, dried over sodium sulphate, filtered and distilled. 6.7 g of an oily residue are recovered. The crude product is taken up in an aqueous solution of methane sulphonic acid. The insoluble matter is separated by extraction with ether and the aqueous phase is rendered alkaline by adding 2N sodium hydroxide solution. The alkaline solution is extracted with ether, and the ether phase is decanted, dried and filtered. After evaporation to dryness, 5.4 g of pure compound are obtained.

For analytical purposes, the product is further purified by recrystallizing it from petroleum ether then from cyclo hexane.

1-[2-(thienyl- 2-thio)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine is obtained in a yield of 58%. This compound melts at 78°.

Analysis $C_{20}H_{26}N_2OS_2$ = 374.57

	C	H	N	S%
Calculated	64.13	7.00	7.48	17.12
Found	64.07	7.05	7.40	17.18

Using the same procedure but starting from 3,4-dimethoxy phenylthiol, 1-[2-(3,4-dimethoxy phenylthio)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine is obtained.

Starting from 4-dimethyl amino phenylthiol, 1-[2-(4-dimethyl amino phenylthio)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine is obtained.

Starting from 3,4-methylene dioxy phenylthiol, 1-[2-(3,4-methylene dioxy phenylthio)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine is obtained.

Starting from 2,5-dimethyl phenylthiol, 1-[2-(2,5-dimethyl phenylthio)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine is obtained.

Starting from 2-ethoxy carbonyl phenyl thiol, 1-[(2-ethoxy carbonyl phenyl thio)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine is obtained.

Starting from 2-methoxy phenyl thiol, 1-[(2-methoxy phenyl thio)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine is obtained.

Starting from 2-methoxy- 5-chloro phenyl thiol, 1-[(2-methoxy- 5-chloro phenyl thio)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine is obtained.

The starting material, 1-(β-chloro ethyl)- 4-(N-phenyl- N-propionyl amino)- piperidine is obtained from 1-(β-hydroxy ethyl)- 4-(N-phenyl- N-propionyl amino)- piperidine by reaction of thionyl chloride; 1-(β-hydroxy ethyl)- 4-(N-phenyl- N-propionyl amino)- piperidine is produced by reacting ethylene oxide with 4-(N-phenyl- N-propionyl amino)- piperidine.

EXAMPLE II

1-[2-(2,6-dimethyl phenyl thio)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine

Step A 2-(2,6-dimethyl phenyl thio)- 1-hydroxy ethane

35 g 2,6-dimethyl thiophenol are dissolved in a solution of 15.6 g sodium hydroxide in 210 ml water, while stirring under an inert atmosphere. After complete dissolution, 34 g chloro ethanol are added portionwise and the milky suspension is then heated to reflux for one hour. The mixture is allowed to cool to room temperature and is extracted three

times with ester to isolate the oily product formed. The ether solutions are washed with wqter, dried over sodium sulphate, filtered and evaporated off. 2-(2,6-dimethyl phenyl thio)- 1-hydroxy ethane is obtained in a yield of 95%. It is used for the next step without any purification.

Step B 2-(2,6-dimethyl phenyl thio)-1-bromo ethane

18.2 g of 2-(2,6-dimethyl phenyl thio)-1-hydroxy ethane and 50 ml chloroform are placed in a flask and when the mixture is perfectly clear, it is cooled to 0°. To the solution, 14.3 g of phosphorous tribromide are added while keeping the temperature to about 0°. After completion of the addition, the temperature is allowed to rise to ambiant temperature and the mixture is then heated to reflux for one hour.

The reaction mixture is then cooled and poured into a mixture of water and ice and the resulting precipitate is extracted with a mixture of ether and chloroform. The organic solutions are separated, washed with a 5% solution of sodium carbonate, then with water, dried over sodium sulphate and evaporated to dryness. A dry residue, weighing 24.2 g is recovered and further purified by distillating it under reduced pressure. 21.2 g of 2-(2,6-dimethyl phenyl thio)-1-bromo ethane are obtained. The yield amounts to 86%. This compound boils at 155°C under 16 mm Hg.

Analysis $C_{10}H_{13}BrS$ = 245.18

	C	H	S	Br%
Calculated	48.99	5.34	13.08	32.59
Found	49.58	5.33	13.22	32.35

Infrared Spectrum : compatible with the proposed structure, lack of starting hydroxy compound.

Step C

1[2-(2,6-dimethyl phenyl thio)- ethyl]-4-(N-phenyl- N-propionyl amino)-piperidine

8.5 g of 2-(2,6-dimethyl phenyl thio)-1-bromo ethane obtained in Step B are dissolved in 200 ml methyl isobutyl ketone. To this solution, 8.1 g of 4-(N-phenyl-N-propionyl amino)- piperidine, 11.2 g anhydrous sodium carbonate and few mg potassium iodide are added and the whole mixture is heated to reflux for 2 hours. The precipitate is then separated by filtration and the filtrate evaporated off. The dry residue, weighing 14.6 g is taken up in the minimum amount of ether to dissolve it. The ether solution is extracted with an N aqueous solution of hydrochloric acid. The hydrochloride of 1-[2-(2,6-dimethyl phenyl thio)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine precipitates and is separated by filtration. It is taken up in water, the aqueous suspension is made basic by adding a 2N solution of sodium hydroxide.

The aqueous phase is extracted with ether three times, the ether solutions are separated, washed with water, dried and evaporated under vacuum.

9.4 g of free base are recovered. It crystallises by scratching from a few drops of isopropyl ether. After further recrystallization from isopropyl ether, a first crop of 1-[2-(2,6-dimethyl phenyl thio)- ethyl]-4-(N-phenyl- N-propionyl amino)-piperidine weighing 6.6 g is obtained. This compound melts at 85°.

Analysis $C_{24}H_{32}OS$ = 396.58

	C	H	N	S%
Calculated	72.69	8.13	7.07	8.09
Found	72.90	7.98	7.06	8.49

Infrared spectrum : in accordance with the structure.
Stretching at 1640 cm^{-1} (tertiary amide)

The starting material, 2,6-dimethyl thiophenol, is produced from *o*.xylidine by diazotation, decomposition of the diazonium salt in the presence of potassium ethyl xanthate and finally decomposing the xanthate by addition of potassium hydroxide then acidifying with a strong acid.

2,6-dimethyl thiophenol boils at 94–96° under 20 mm Hg.

Analysis $C_8H_{10}S$ = 138

	C	H	S%
Calculated	69.52	7.29	23.20
Found	69.80	7.49	

EXAMPLE III

1—(2—phenylthioethyl)—4—(N—phenyl—N—propionylamino)—piperidine

Using the procedure described in Example II and starting from thiophenol there are successively obtained:

– 2–phenylthio–1–hydroxyethane,
– 2–phenyltjio–1–bromoethane, BP = 132–136°C/13 mm Hg.

Analysis $C_8H_9Br\,S$ = 217.12

	C	H	S	Br%
Calculated	44.26	4.18	14.76	36.80
Found	44.58	4.20	15.00	36.41

– 1–(2–phenylthioethyl)–4–(N–phenyl–N–propionylamino)–piperidine.

Its hydrochloride melts at 183°C. It is fairly soluble in water.

EXAMPLE IV

1—(2—2,6—dichlorophenylamino)—ethyl]—4—(N—phenyl—N—propionyl—amino)—piperidine

Using the procedure described in Example II and starting from 2,6-dichloro aniline, there are successively obtained:

– N-(2-hydroxy ethyl)- 2,6-dichloro aniline,
– N-(2-bromoethyl)- 2,6-dichloro aniline,
– 1-[2-(2,6-dichloro phenyl amino)-ethyl]- 4-(N-phenyl- N-propionyl amino)-piperidine which melts at 82–84°C (from petroleum ether).

Analysis $C_{22}H_{27}Cl_2ON_3$ = 420.38

Calculated	62.85	6.47	9.99	16.86
Found	63.10	6.57	9.97	16.68

Infrared spectrum : compatible with the proposed structure,
stretchings at 3320 cm^{-1} (—NH—group)
stretchings at 1640 cm^{-1} (carbonyl of a tertiary amide)

EXAMPLE V

1—[2—(2,6—dimethylphenylamino)—ethyl]—4—(N—phenyl—N—propionyl—amino)—piperidine

Using the procedure described in Example II but starting from o - xylidine there are successively obtained: —N—(-hydroxyethyl)-2,6-dimethyl aniline
BP = 105-110°C/0.15 mm Hg,
– N–(β–bromoethyl)–2,6–dimethyl aniline hydrobromide,
MP = 240–250°C (sublim.).

Analysis $C_{10}H_{14}NBr$, BrH = 309.06

	C	H	N	Br%
Calculated	38.86	4.89	4.53	51.71
Found	38.98	5.17	4.64	51.60

– 1–[2–(2,6–dimethylphenylamino)–ethyl]–4–(N–phenyl–N–propionylamino)–piperidine

It melts at 68–70°C. It is soluble in the stoechiometric amount of methanesulphonic acid giving the methanesulphonate after evaporation of the solvent.

Analysis $C_{24}H_{33}N_3O$ = 379.55

	C	H	N%
Calculated	75.94	8.76	11.07
Found	75.55	8.52	11.00

EXAMPLE VI

1-[2-(N-phenyl- N-methyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine

Using the procedure described in Example II but starting from N-methyl aniline there are produced:
– N-(β-hydroxy ethyl)- N-methyl aniline,
– N-(β-chloro ethyl)- N-methyl aniline,
– 1-[2-(N-phenyl- N-methyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine.

It melts at 88–90°C (from isopropyl ether).

The compound is soluble in an aqueous solution of methane sulphonic acid.

Analysis $C_{23}H_{31}N_3O$ = 365.52

	C	H	N%
Calculated	75.57	8.54	11.49
Found	75.70	8.51	11.41

The same compound may also be produced from 1-[(2-phenyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine by methylation with a mixture of formol and formic acid.

EXAMPLE VII

1-[2-(phenyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine

Using the procedure described in Example II the following compounds have been obtained, starting from aniline:

- N-(β-hydroxy ethyl)- aniline,
- N-(β-bromo ethyl)- aniline,
- 1-[2-(phenyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine.

This compound melts at 74–76°C. It is soluble in hydrochloric acid and in a solution of methane sulphonic acid in a mixture of water and propylene glycol.

Analysis $C_{22}H_{29}N_3O$ = 351.49

	C	H	N%
Calculated	75.17	8.31	11.95
Found	75.06	8.50	11.94

EXAMPLE VIII

1-[2-(N-acetyl- N-phenyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine.

By reaction of excess acetic anhydride with 1-[2-(phenyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine, there is obtained 1-[(N-phenyl- N-acetyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine. It melts at 146°C (from cyclohexane). It is soluble in hydrochloric acid.

Infrared spectrum :

- absence of stretching corresponding to the group –NH–
- presence of a more intense carbonyl band at 1640 cm^{-1}

Analysis $C_{24}H_{31}N_3O_2$ = 393.53

	C	H	N%
Calculated	73.25	7.95	10.67
Found	73.49	8.05	10.69

Using the same procedure but starting from 1-[2-(2,6-dimethyl phenyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine and butyryl chloride, 1-(2-[N-(2,6-dimethyl phenyl)- N-butyryl amino]- ethyl)- 4-(N-phenyl- N-propionyl amino)- piperidine is obtained.

Similarly, using dipropyl acetyl chloride as the acylating agent, 1-(2-[N-(2,6-dimethyl phenyl)- N-dipropyl acetyl amino]- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine is obtained.

EXAMPLE IX

1-[2-(N-phenyl- N-allylamino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine

Using the procedure described in Example II and starting from aniline, the following compounds are produced:

- N-allyl aniline,
- N-allyl- N-(β-hydroxy ethyl)- aniline,
- N-allyl- N-(β-bromo ethyl)- aniline
- 1-[2-(N-phenyl- N-allyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine.

The title compound may also be obtained starting from N-allyl aniline, by reaction with sodium in liquid ammonia, then reaction of the sodium derivative with 1-(β-chloro ethyl)- 4-(N-phenyl- N-propionyl amino)- piperidine.

EXAMPLE X

cis dl 1-[2-(2,6-dimethyl phenyl amino)- ethyl]- 3-methyl- 4-(N-phenyl- N-propionyl

amino)- piperidine

By reacting an excess of propionic anhydride with 2.7 g of *cis* dl 3-methyl- 4-phenyl amino- piperidine, 2.6 g of *cis* dl 3-methyl- 4-(N-phenyl- N-propionyl amino)- piperidine are obtained. The latter is condensed with N-(β-bromo ethyl)- amino- 2,6-dimethyl benzene to produce *cis* dl 1-[2-(2,6-dimethyl phenyl amino)- ethyl]- 3-methyl- 4-(N-phenyl- N-propionly amino)- piperidine.

EXAMPLE XI

Pharmacological tests

(a) *acute toxicity*

The average lethal dose of the compounds has been determined on batches of male mice Swiss strain weighing about 20 g. They receive the compound to be tested either intraperitoneally in suspension in an aqueous solvent or orally dissolved in an aqueous solution of gum arabic.

The animals are kept under survey for 8 days and the deaths, if any, are recorded for each batch. The average lethal dose is calculated graphically according to the method described by Tainter and Miller.

Intraperitoneally the average lethal dose ranges from 30 to 200 mg/kg, depending on the compound.

Orally, the average lethal dose ranges from 250 to 1000 mg/kg.

(b) *hypotensive activity*

The compounds have been administered to batches of normal dogs, previously anaesthetized with Nembutal, at increasing doses ranging from 0.5 to 5 mg/kg. Depending on the tested compound, the mean arterial pressure is decreased by from 20 to 40% and the cardiac rhythm is reduced by from 30 to 40%. The duration of both effects lasts for from 20 to 45 minutes.

(c) *neurological effect*

In mice (CD strain) the first active doses on the central nervous system is from 5 to 10 mg/kg intraperitoneally. At this dose the only effect is a slight increase of motility. At a dose of 25 mg/kg intraperitoneally the neurological effects are still very limited (slight increase in muscular tone, decrease of the sensibility and the reflexes). In cats the only effects are a decrease in the reflexes and in the muscular strength.

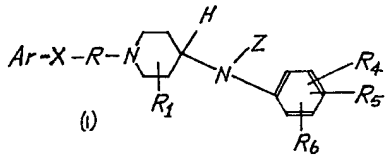
Upon oral administration, the neurological effects are still more attenuated. The first orally active dose in mice is about 50 mg/kg and induces a slight increase of muscular tone.

At a dose of 100 mg/kg orally, the respiration is slightly depressed, and mydriasis appears. Higher doses cause death.

It may therefore be stated that the compounds of the invention do not induce any significant effect on the central nervous system. They are neither neuro-depressant nor depressant of the respiratory center to any significant degree.

WHAT WE CLAIM IS:–

1. A compound of the general formula



(I)

in which

R_1 is a hydrogen atom or a lower alkyl group;

R is an alkylene chain having from 2 to 4 carbon atoms which may be substituted with one or more lower alkyl groups;

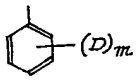
X is a sulphur atom or a group $-N(R_2)-$ in which R_2 is a hydrogen atom, a lower alkyl carbonyl group, a lower alkenyl group or a lower alkyl group;

Z is the acyl group from an alkyl carboxylic acid having up to 10 carbon atoms;

each of R_4, R_5 and R_6, which are the same or different, is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group or a lower alkylene dioxy group; and

Ar is

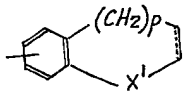
(a) a phenyl group of the general formula



in which each D is a halogen atom or a lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, lower alkylthio, carboxy, lower aldoxy carbonyl, nitro, amino, lower alkyl amino, di(lower alkyl) amino, lower acylamino, sulphon amido, lower alkylamino sulphonyl, di(lower alkyl) amino sulphonyl, lower alkyl sulphonyl, amino carbonyl, cyano, trifluoro methyl or lower alkylene dioxy group, and

m is 0 or an integer from 1 to 5;

(b) a bicyclic group of the general formula

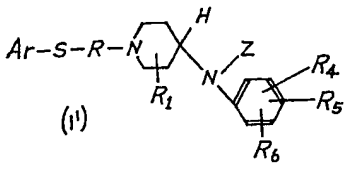


in which X′ is an imino radical NH and *p* is 0, 1 or 2, or

X′ is a sulphur atom and *p* is an integer from 1 to 3 and the broken line indicates an optional double bond; or

(c) a thienyl group which may be substituted with a lower alkyl group.

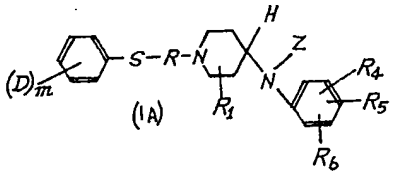
2. A compound according to claim 1 of the general formula



(I')

in which Ar, R, Z, R_1, R_4, R_5 and R_6 have the meanings specified in claim 1.

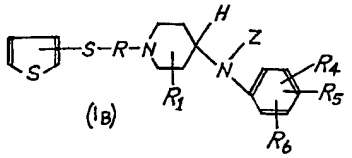
3. A compound according to claim 1 of the general formula



(IA)

in which D, R, R_1, Z, R_4, R_5, R_6 and *m* have the meanings specified in claim 1.

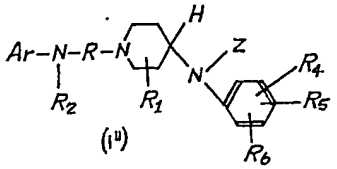
4. A compound according to claim 1 of the general formula



(IB)

in which R, R_1, Z, R_4, R_5 and R_6 have the meanings specified in claim 1.

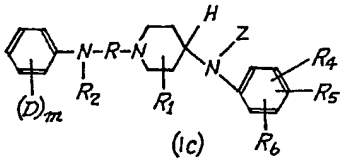
5. A compound according to claim 1 of the general formula



(I'')

in which Ar, R, R_1, R_2, R_4, R_5, R_6 and Z have the meanings specified in claim 1.

6. A compound according to claim 1 of the general formula



(IC)

in which D, R, R_1, R_4, R_5, R_6, Z and *m* have the meanings specified in claim 1 and

R_2 is a hydrogen atom or a methyl, ethyl, allyl or acetyl group.

7. 1-[2-(Thienyl- 2-thio)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine.

8. 1-[2-(2,6-Dimethyl phenyl thio)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine.

9. 1-[2-(Phenyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine.

10. 1-[2-(N-phenyl- N-methyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine.

11. 1-[2-(2,6-Dichloro phenyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine.

12. 1-[2-(N-phenyl- N-acetyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine.

13. 1-[2-(2,6-Dimethyl phenyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine.

14. 1-[2-(N-phenyl- N-allyl amino)- ethyl]- 4-(N-phenyl- N-propionyl amino)- piperidine.

15. A compound according to any one of claims 1 to 6 in the form of an optically-active isomer or diastereo isomer.

16. An acid addition salt of a compound according to any one of claims 1 to 15.

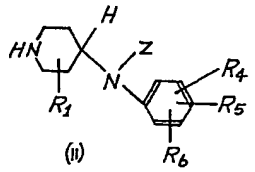
17. A salt according to claim 16 which is physiologically tolerable.

18. A pharmaceutical composition comprising as active ingredient at least one compound according to claim 1 or a physiologically tolerable acid addition salt thereof in admixture of conjunction with a pharmaceutically suitable carrier.

19. A pharmaceutical composition according to claim 18 which is in a form suitable for oral, parenteral, sublingual or rectal administration.

20. A pharmaceutical composition according to claim 18 or claim 19 which contains the active ingredient in an amount of from 1 to 250 mg per unit dosage.

21. A process for preparing a compound according to claim 1 which comprises reacting a 4-amino piperidine of the formula



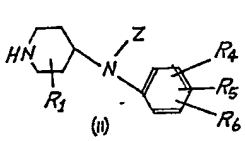
(II)

in which R_1, R_4, R_5, R_6 and Z have the meanings specified in claim 1, with a compound of the formula

Ar – X – R – Y

in which Ar, X and R have the meanings specified in claim 1, and Y is a halogen atom or the acyl radical of a lower alkyl-or an aryl- sulphonic acid.

22. A process for preparing a compound according to claim 1 which comprises reacting a 4-amino piperidine of the formula

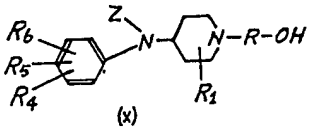


(II)

in which R_1, Z, R_4, R_5 and R_6 have the meanings specified in claim 1, with a compound of the formula

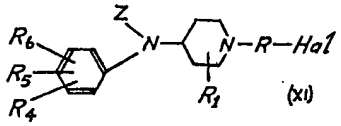
Y – R – OH

in which R and Y have the meanings specified in claims 1 and 21, respectively, to form a 4-amino piperidino- alkanol of the formula



(x)

submitting the latter to the action of a halogenating agent to produce the corresponding halide of the formula



(xi)

in which Hal is a halogen atom,
and reacting the latter with an aryl derivative of the formula

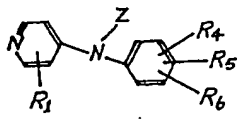
Ar – X – H

in which Ar and X have the meanings specified in claim 1.

23. A process for preparing a compound according to claim 1 which comprises condensing an arylalkyl ester of the formula

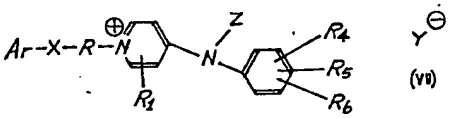
Ar – X – R – Y

in which Ar, X, R and Y have the meanings specified in claim 1, with a 4-amino pyridine of the formula



(vi)

in which R_1, Z, R_4, R_5 and R_6 have the meanings specified in claim 1,
to produce a pyridinium salt of the formula



(vii)

and reducing the latter by catalytic hydrogenation or with an alkali metal complex hydride.

24. A process for preparing a compound according to claim 1 carried out substantially as described in any one of Examples I to X herein.

25. A compound according to claim 1 whenever prepared by a process according to any one of claims 21 to 24.

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